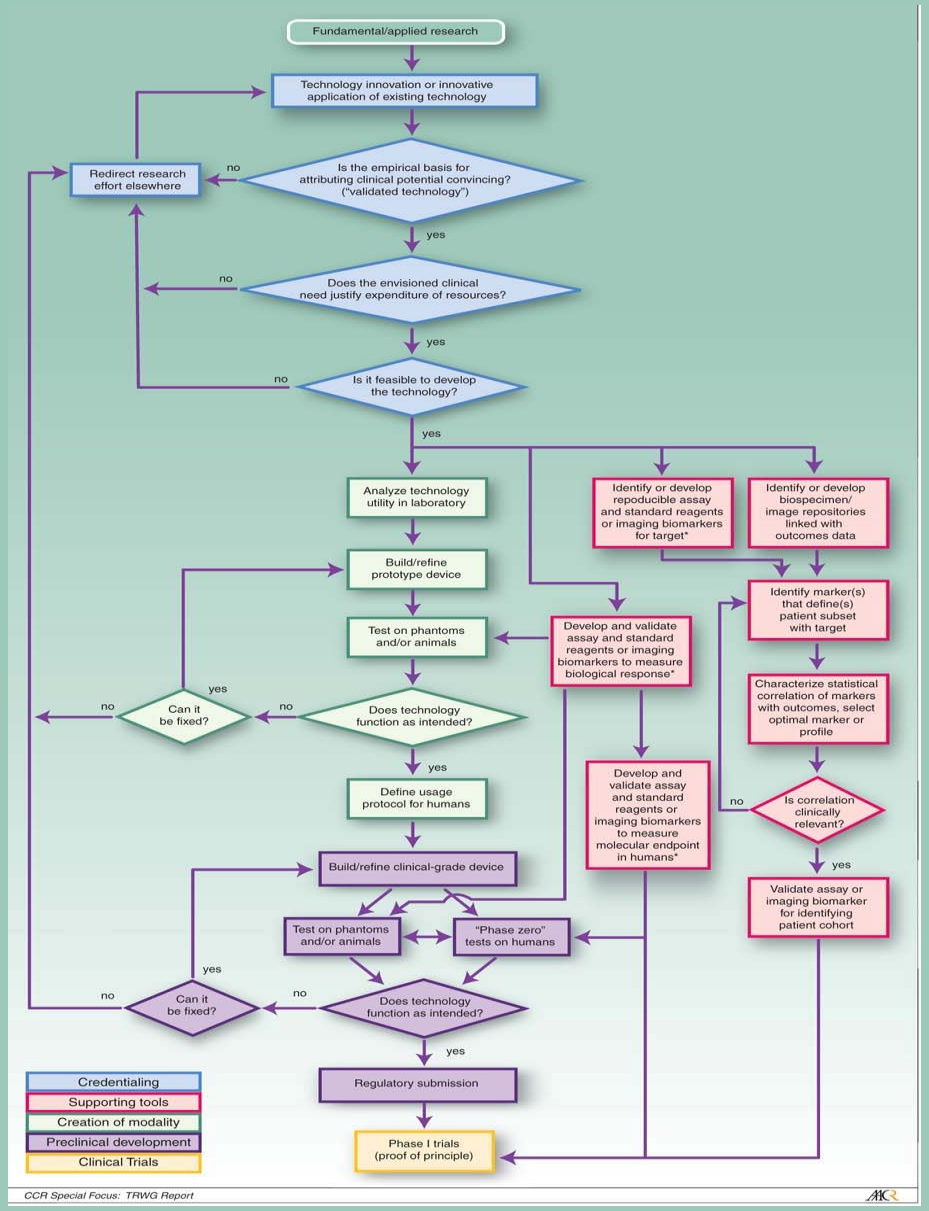
Interventive Devices Pathway Example

Sunday, November 9, 2008

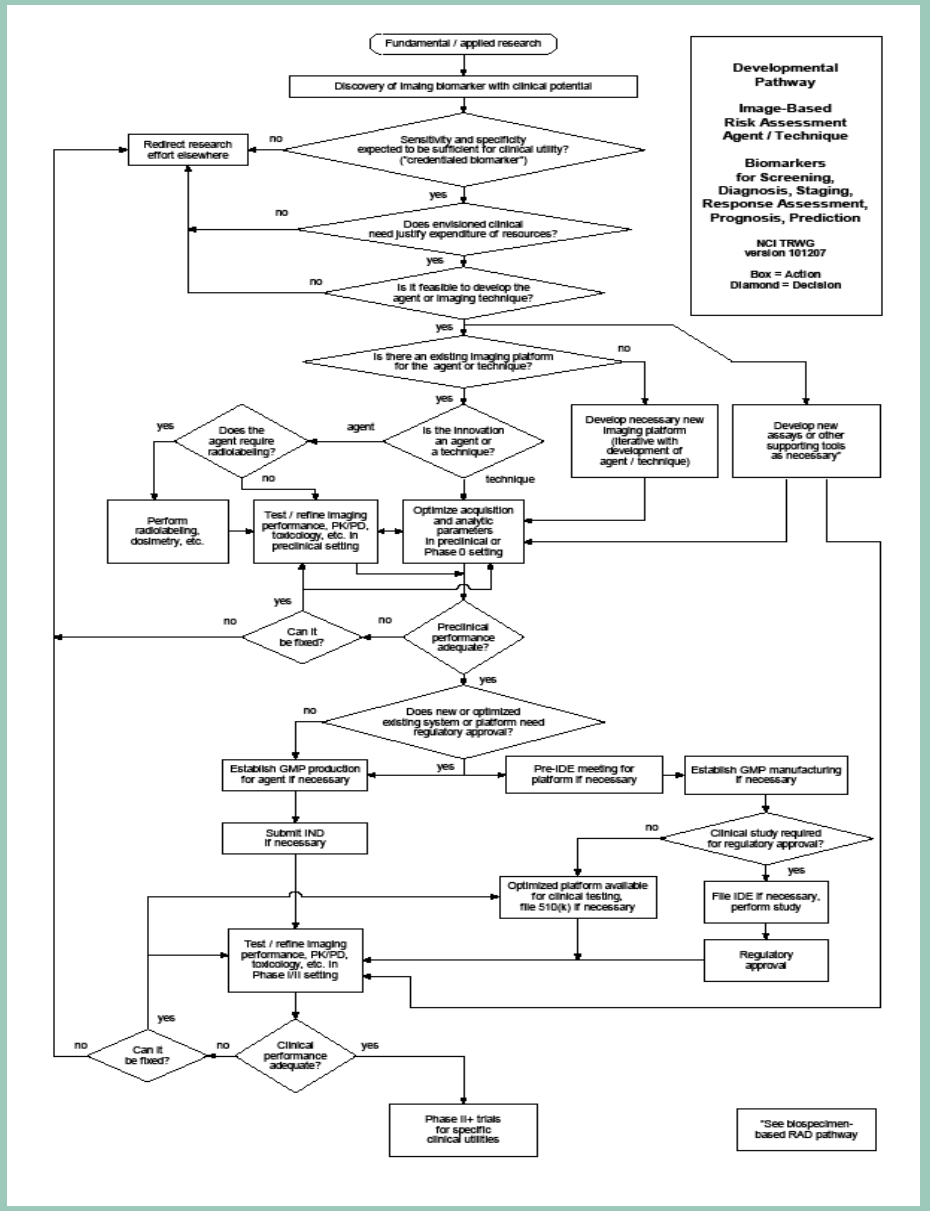
Interventive Devices Pathway:
Example for Discussion Purposes

Development, Optimization, and Validation of
Irreversible Electroporation (IRE)
Integrated with
Imaging Planning, Guidance, and Monitoring
for the Treatment of
Hepatocellular Carcinoma
(or perhaps Pancreatic Cancer based on CA and Rx Characteristics)

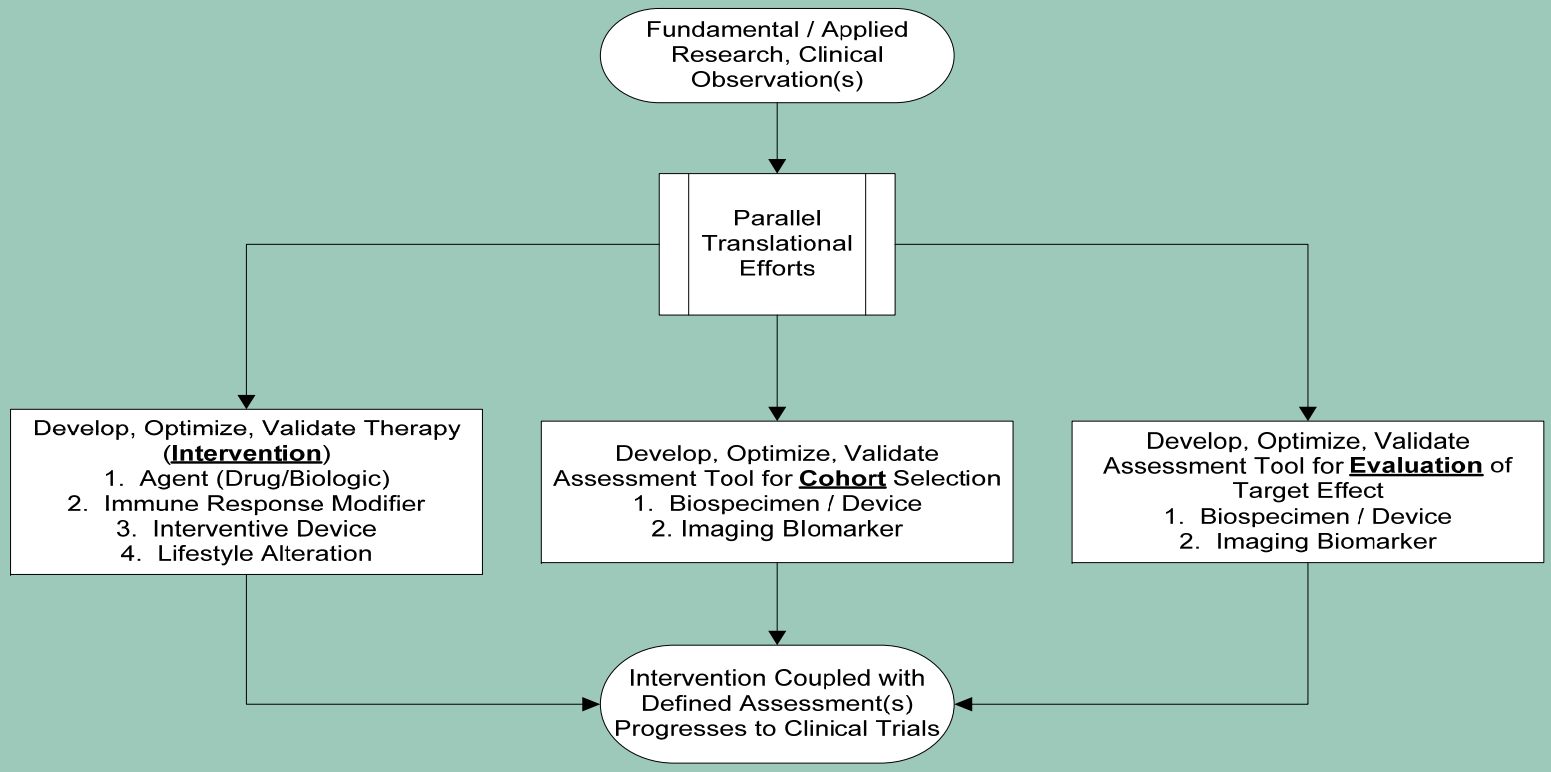
Interventive Device



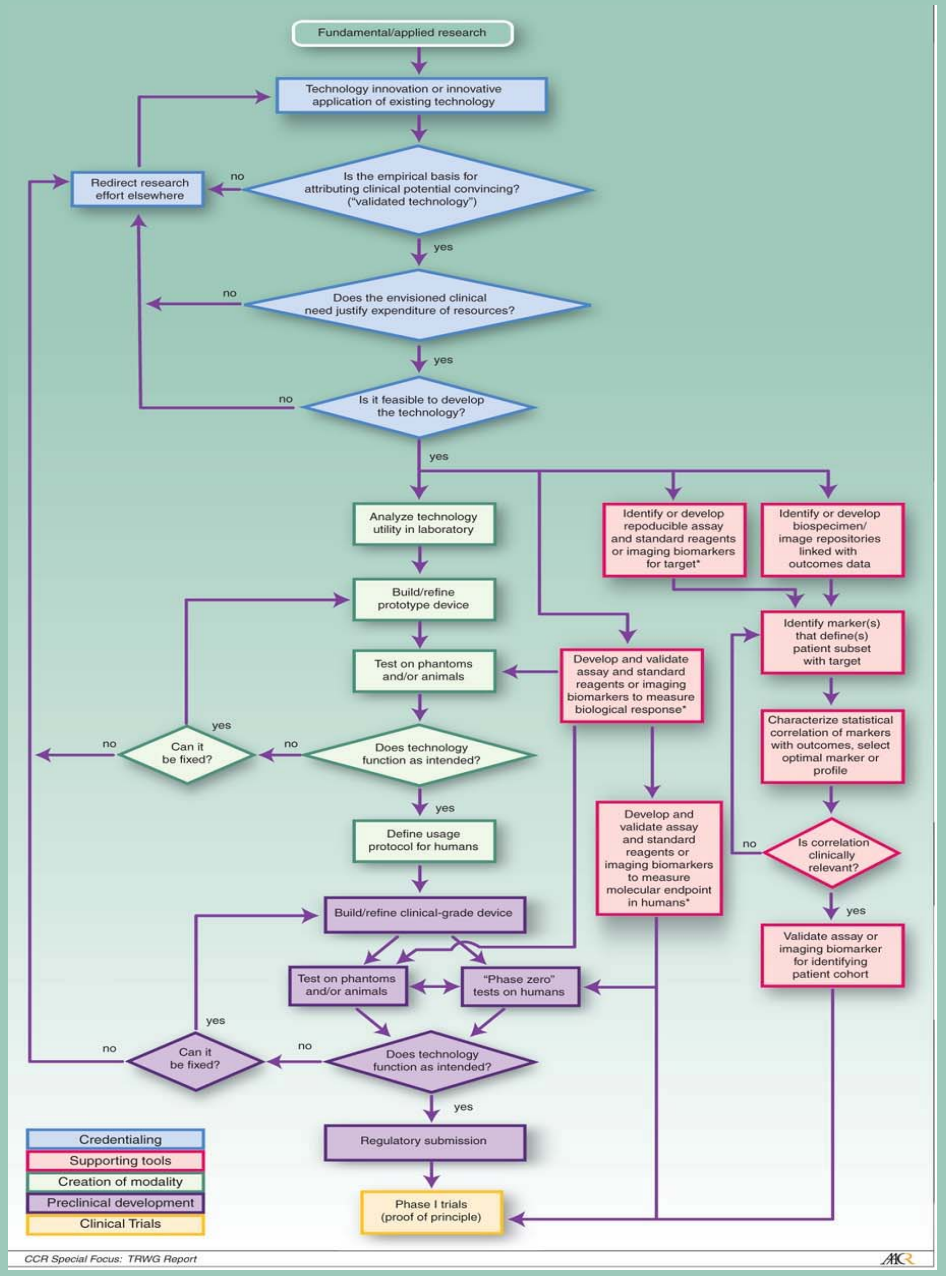
Imaging Agent / Technique (Biomarker)



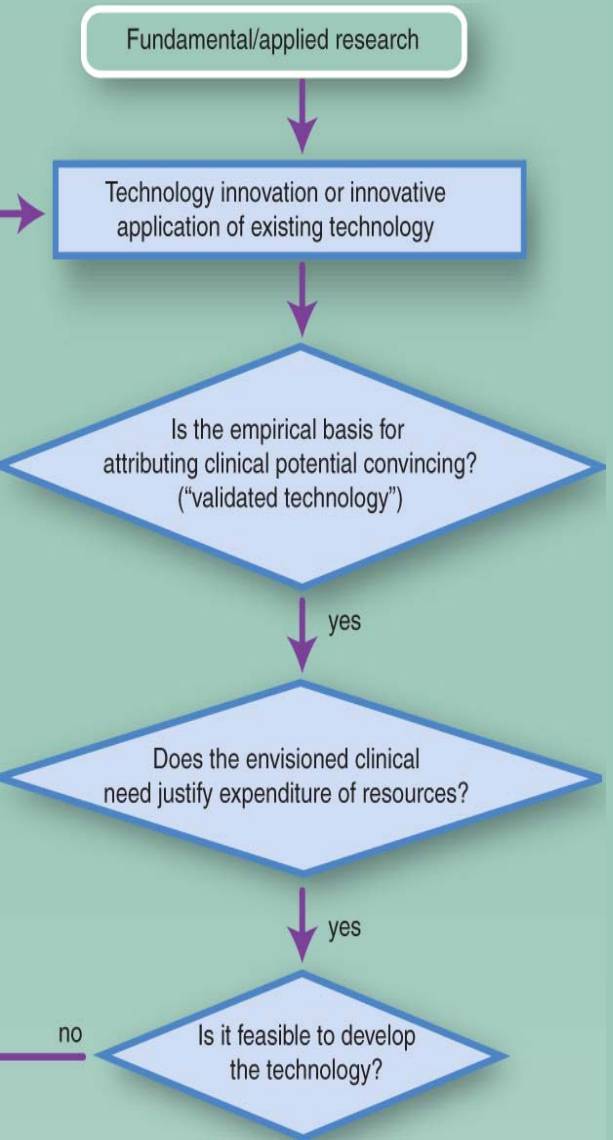
High Level Overview of Translational Research Development Pathways (ICE)



Interventive Device

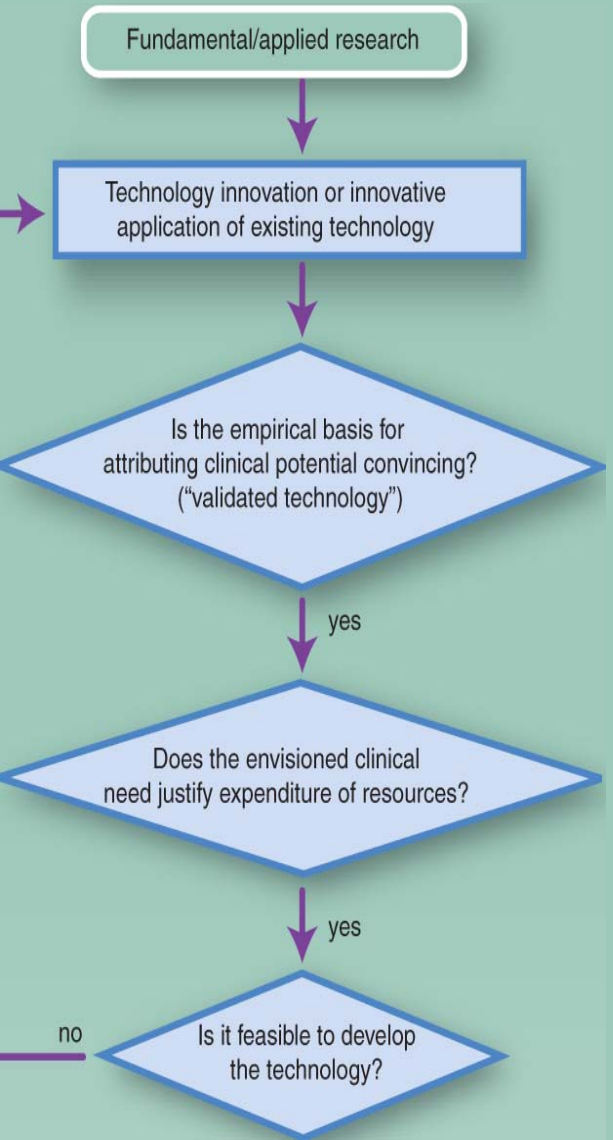


Interventive Devices Pathway:
Credentialing: Scientific validation - 1



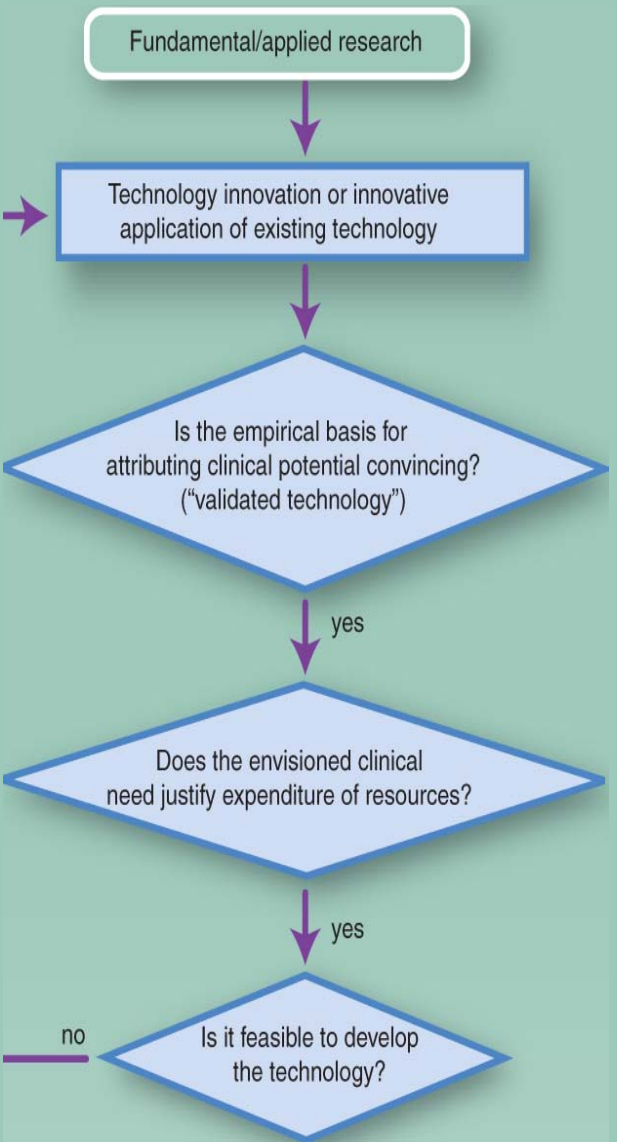
- IRE creates microscopic pores in the cell membrane through the application of ms-long, high-voltage electrical pulses
- Leads to inability to maintain cellular homeostasis
- Cell death through apoptosis over 24-hour period (rather than "immediate" thermal effect)
- Not susceptible to heat sink effect

Interventive Devices Pathway:
Credentialing: Scientific validation - 2



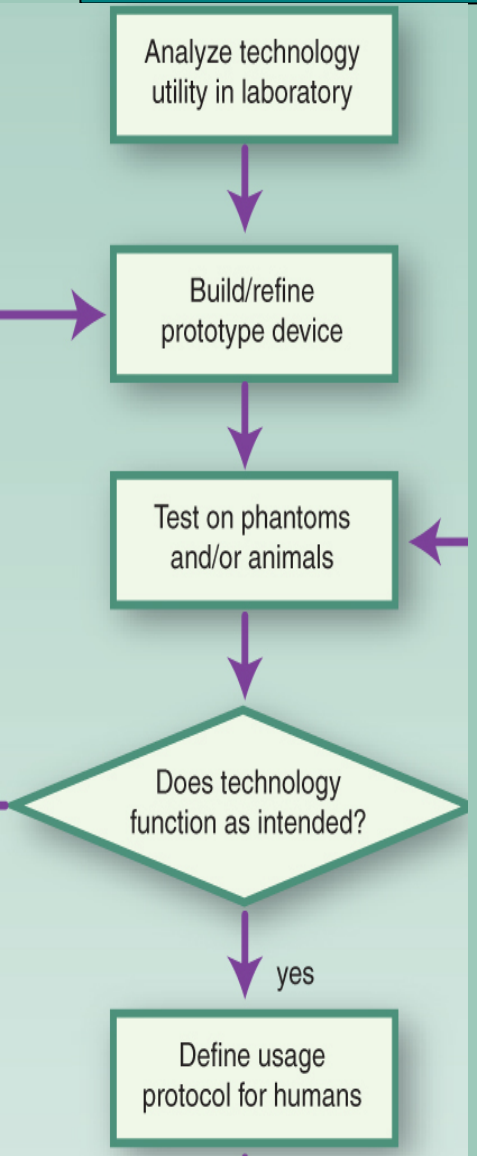
- Predictable ablation zone determined by physics of electric fields (calculable and able to be modeled) — demonstrated *in vitro* and *in vivo* porcine studies
- Purportedly preserves underlying collagenous structures, therefore
- Theoretically may be used adjacent to vessels, nerves, intestines, vital organs, etc.
- Short treatment times (seconds rather than minutes/hours)

Interventive Devices Pathway:
Credentialing: Clinical need



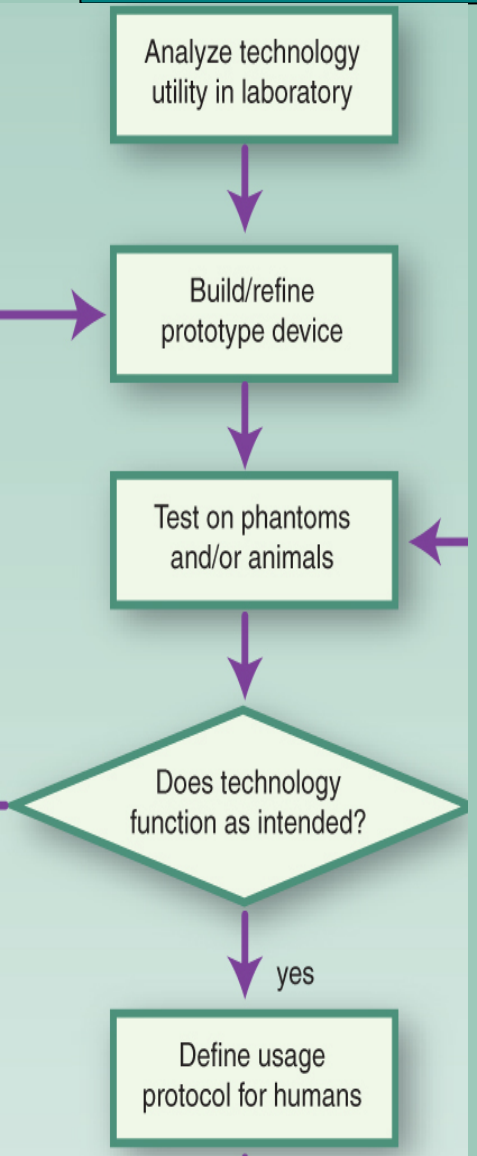
- The majority of "cures" in solid tumors involve excision coupled with systemic therapy (±RT)
- Targeted systemic therapy will likely be coupled with less invasive (i.e., targeted local-regional) therapies rather than open excision
- HCC is increasing in prevalence
- The majority of patients with HCC cannot have curative excision
- Potential pancreatic application

Interventive Devices Pathway:
Creation of Modality - 1



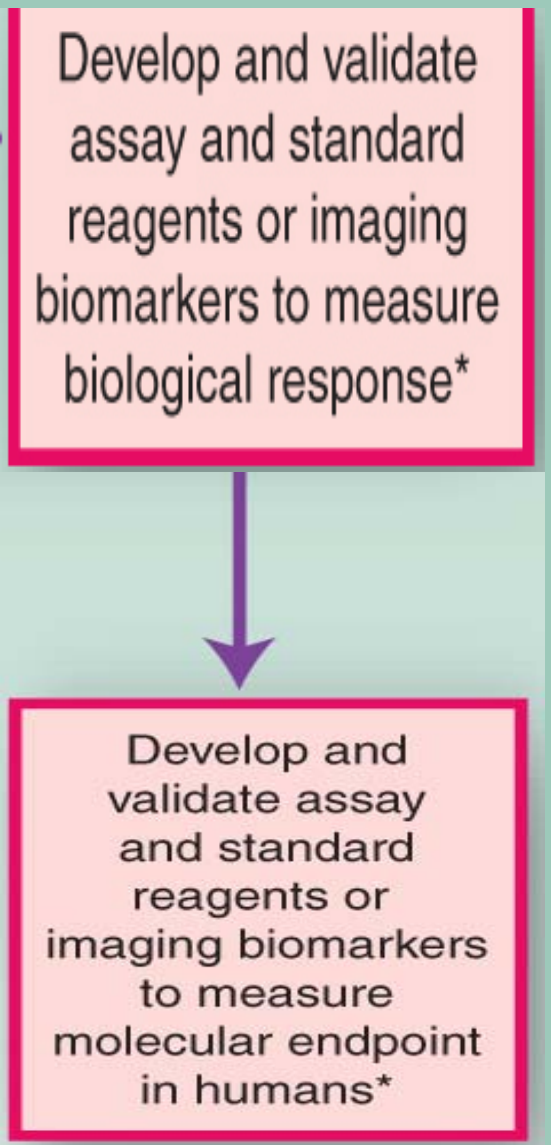
- IRE devices currently available for clinical use (510k), but not fully optimized and without tight imaging integration (Angiodynamics)
- New modality includes IRE tightly integrated with imaging for planning, guidance, and monitoring (including detection of end-point — see also supporting tools) & guidance tools
  - IG Liver Surgery, MRI-guided Breast Bx, 3D-US Guidance; Stefansic, Nevo, Burdette
- Monitoring complicated by delayed cell death

Interventive Devices Pathway:
Creation of Modality - 2



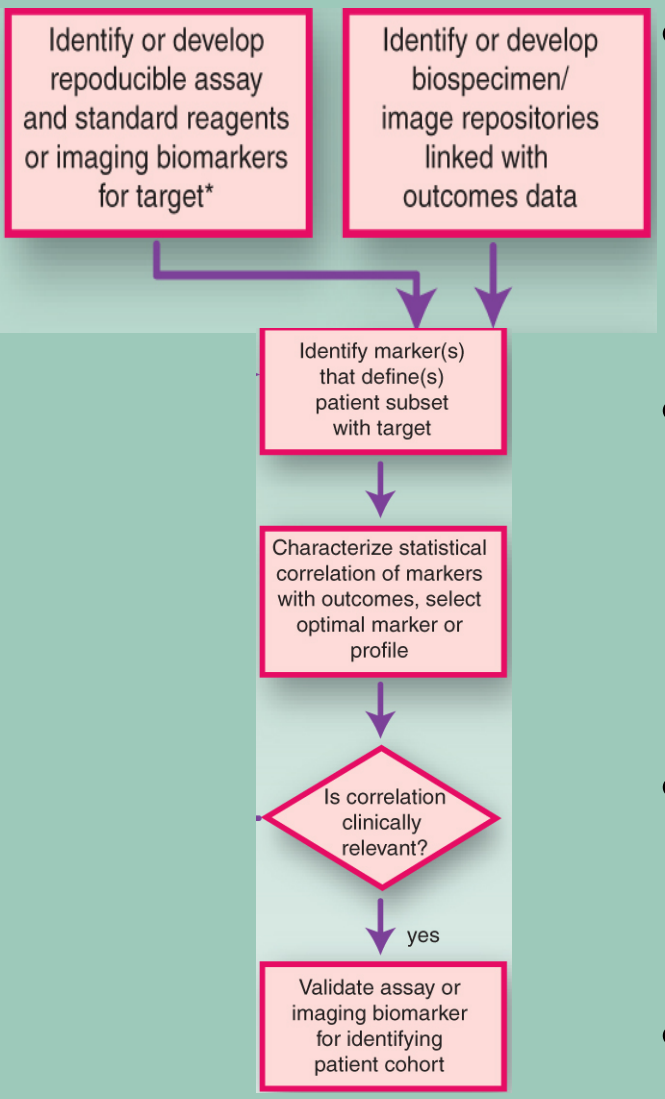
- Ablations in phantoms, isolated organ preparations, and animals necessary to (borrow from the MRgFUS model):
  - Validate claims of safety to adjacent structures under specific energy and physiologic/biologic conditions
  - Optimize performance so as to take maximum advantage of IRE physical properties in the *in vivo* biologic environment
  - Evaluate imaging options (CT, MRI, PET, multimodality fusion, etc.) for tight integration

Interventive Devices Pathway:
Supporting tools — Cohort ID & Response



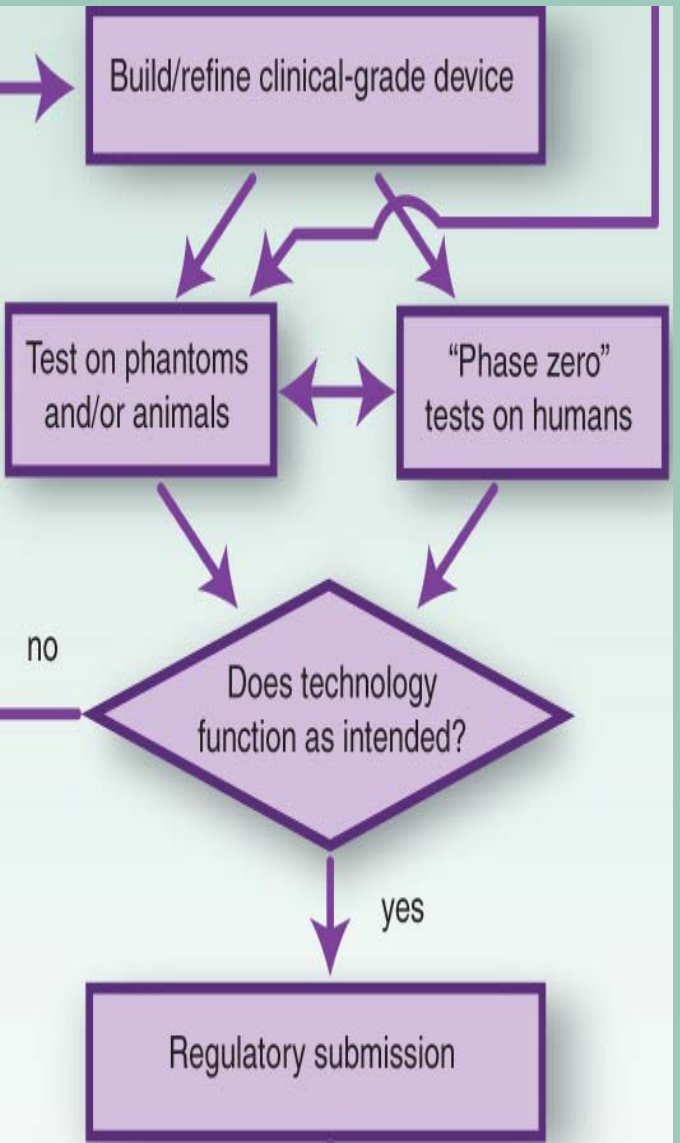
- Multiple modalities coupling anatomic and physiologic parameters likely necessary (potentially including AFP as a device-based *in vitro* test?)
  - Must Evaluate Both Targeted Effect & Residual Viable Tumor Cells
- ApoSense to image early commitment to apoptotic death?
- MRI to image alterations in pH, diffusion/permeability?
- Nanoparticle agents to assess cell membrane porosity?

Interventive Devices Pathway:
Supporting tools — Cohort ID & Response



- Imaging of residual viable tumor and/or couple anatomic imaging with sensitive circulating *in vitro* biomarker for viable HCC
- Develop biospecimen repository from HCC patients treated by excision, ablation, systemic Rx & correlate with imaging tools
- Develop necessary sampling tools
  - Optical Bx, Magnetic Bx Needle/Cell Selection; Follen, Flynn
- Partner with Assessment Modalities

Interventive Devices Pathway:
"Preclinical" Development



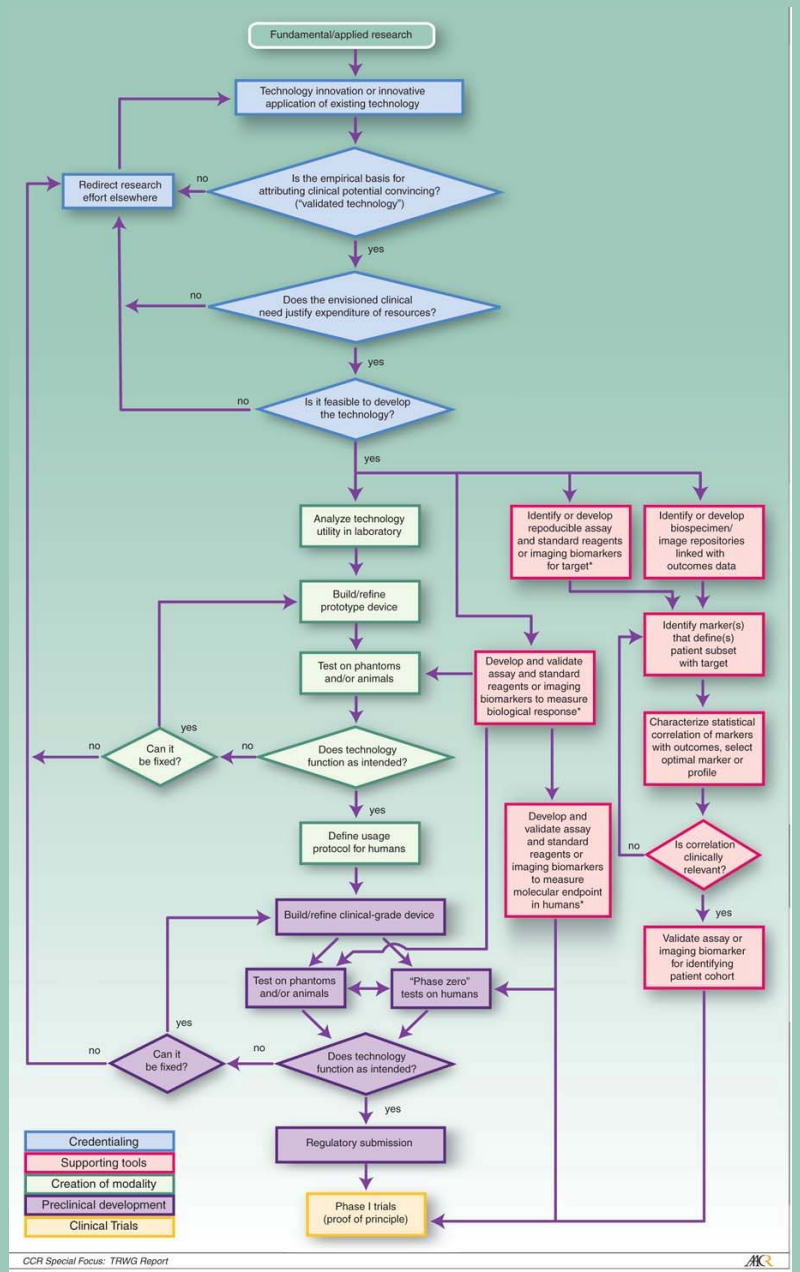
- Partner with IRE & imaging industry co-developers in the "Creation of Modality" phase
- Liver ablation perfused-phantom developed by Dodd
- Utilize modality in multimodality environment such as AMIGO in "Phase 0" setting
  - Resource for IDT at B&W; Hata/Jolesz
- Optimize system performance
  - Interventive Devices (& Imaging Assessment Modalities) require clinical use in "Preclinical" Development

Interventive Devices Pathway:
Clinical Trials

Phase I trials
(proof of principle)

- Perform “dose-escalation” trials for safety in c/w image-based planning, guidance, and monitoring as a system with secondary endpoint of validating the biomarker(s) for residual tumor — ablate and resect/transplant or ablate, Bx, and follow
- For ablate and follow, obtain tissue pre- and post-Rx for biologic correlation potentially using novel biopsy and cell separation tools

Interventive Device Pathway



- Less invasive, targeted local-regional therapies coupled with targeted systemic therapies for HCC
- Integrated system
- Technically feasible
- Alter paradigm of validation & optimization
- Imaging is part of modality **&** a supporting tool (perhaps coupled with *in vitro* test
- FDA should be included in development and approval paradigm early (atypical)
- Hand-offs/Collaborations
- Mimic agent Phase I – III